How proteomics shed light in understanding host-parasite interplay and clinical consequences during trypanosome infectious process

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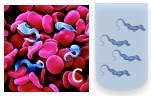
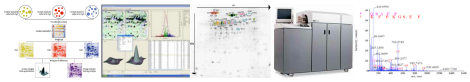
Background and aims:

Animal trypanosomosis is a major constraint to livestock productivity in the tropics and has a significant impact on the life of millions of people. In Africa, South America and south east Asia, the disease is caused mainly by *Trypanosoma congolense* (A), *T. evansi* (B), *T. vivax* and *T. brucei brucei*.

The extracellular position of trypanosomes in the bloodstream of their host (C) requires consideration of both the parasite and its naturally excreted-secreted factors (secretome) in the course of pathophysiological processes (anemia, cachexia, neurological disorders). We therefore developed and standardised a method to produce purified secretomes of African trypanosomes[1].



Workflow and results:

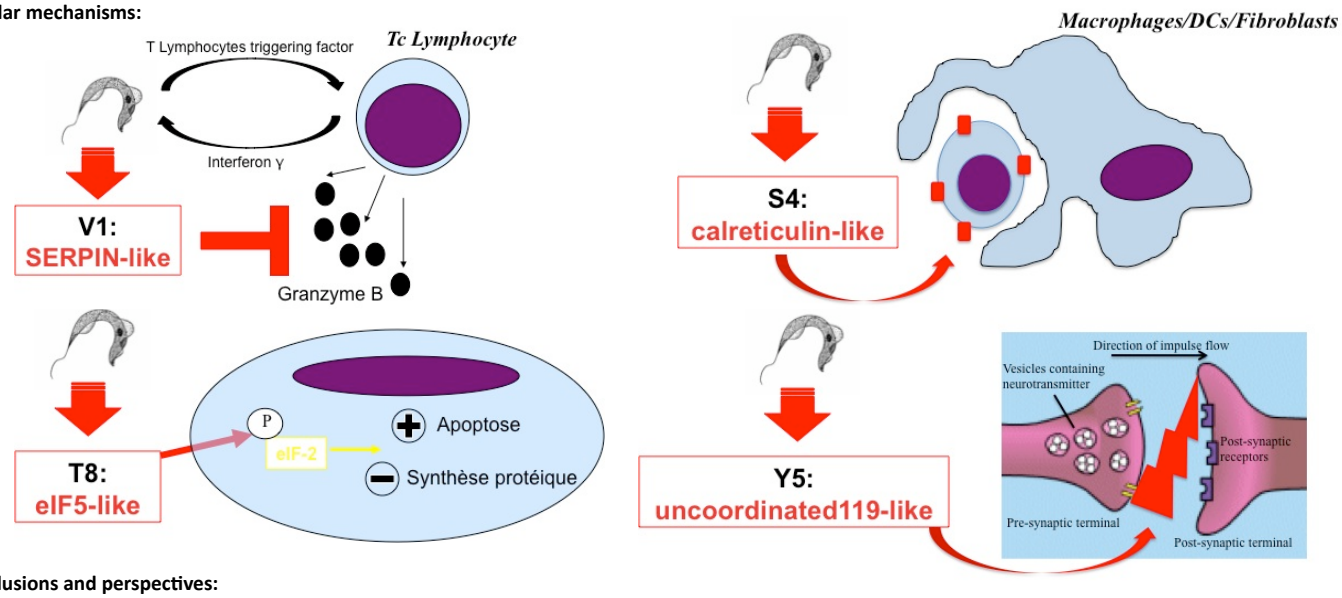


We used 2D-DIGE and statistical differential analysis (Progenesis SameSpot ®) coupled to Nano HPLC ESI-Q-TOF to propose for the first time a comparative approach of the secretomes of *T. congolense* and *T. evansi* clones exhibiting marked differences in their virulence and pathogenicity profiles.

Surprisingly, the 2D-DIGE-MS/MS analytical filter highlighted few differentially expressed molecules, some of which were moreover identified as *Putative Uncharacterised Protein*[2]. Nevertheless and interestingly, bioinformatics allowed us to directly link several proteins to the clinical disorders observed in trypanosome-infected animals in the field.

Secreted protein	Trypanosoma species	Peptides/%cover/ Mowse score	Propsearch server data	Hypothetical function	Link with clinical disorders
V1	*T. congolense*	6 / 36 / 276	Serine protease inhibior 2.4 precursor	*B-SERPIN B9 → inhibitor/regulator of granzymes*[3] *, protection of trypanosomes from T cytotoxic lymphocytes activated by TLTF*[4]	Immuno-suppression, Trypanosome development
T8	*T. congolense*	4 / 21 / 132	Eukaryotic translation initiation factor 5	*eIF-5 dicrease protein synthesis and increase apoptosis via eIF-2 phosphorylation*[5]	Immuno-suppression
S4	*T. congolense* *T. evansi*	4 / 23 / 129 31 / 43 / 329	Calreticulin precursor	*Calreticulin binds to cell surface and permits engulfment of live cells*[6]	Immuno-suppression, Autoimmunity
Y5	*T. evansi*	7 / 31 / 147	Neurotransmission inhibitor, (Hemolysin)	*UNC-119 is located in neuron cell bodies and acts cell-autonomously to inhibit axon branching*[7]	Neurological disorder (Anemia)

Cellular mechanisms:



Conclusions and perspectives:

This first comprehensive analysis shows how proteomics is powerful in the molecular identification of differentially expressed trypanosomes molecules correlated with either the virulence process or exhibiting potential properties to induce pathogenic dysregulation of physiological functions. Moreover, deciphering of the molecular dialogues and conflicts that govern host-parasite interplay is promising to define new molecular targets for improved field diagnosis and new strategies of interference with the infectious process to fight against animal trypanosomosis.

References:

[1] Holzmuller P, Grébaut P, Peltier JB, Brizard JP, Perrone T, Gonzatti M, Bengaly Z, Rossignol M, Aso PM, Vincendeau P, Cuny G, Boulangé A, Frutos R. Secretome of animal trypanosomes: From a Standard Method toward New Diagnostic and Therapeutic Targets. *Ann N Y Acad Sci*. 2008 Dec;1149:337-42; [2] Grébaut P, Chuchana P, Brizard JP, Demettre E, Seveno M, Bossard G, Jouin P, Vincendeau P, Bengaly Z, Boulangé A, Cuny G, Holzmuller P. Identification of total and differentially expressed excreted-secreted proteins from *Trypanosoma congolense* strains exhibiting different virulence and pathogenicity. *Int J Parasitol*. 2009 Aug;39(10):1137-50; [3] Kaiserman D, Bird PI. Control of granzymes by serpins. *Cell Death Differ*. 2010 Apr;17(4):586-95; [4] Olsson T, Bakhiet M, Edlund C, Höjeberg B, Van der Meide PH, Kristensson K. Bidirectional activating signals between Trypanosoma brucei and CD8+ T cells: a trypanosome-released factor triggers interferon-gamma production that stimulates parasite growth. *Eur J Immunol*. 1991 Oct;21(10):2447-54; [5] Jennings MD, Pavitt GD. eIF5 has GDI activity necessary for translational control by eIF2 phosphorylation. *Nature*. 2010 May 20;465(7296):378-81; [6] Gold LI, Eggleton P, Sweetwyne MT, Van Duyn LB, Greives MR, Naylor SM, Michalak M, Murphy-Ullrich JE. Calreticulin: non-endoplasmic reticulum functions in physiology and disease. *FASEB J*. 2010 Mar;24(3):665-83. [7] Knobel KM, Davis WS, Jorgensen EM, Bastiani MJ. UNC-119 suppresses axon branching in C. elegans. *Development*. 2001 Oct;128(20):4079-92.